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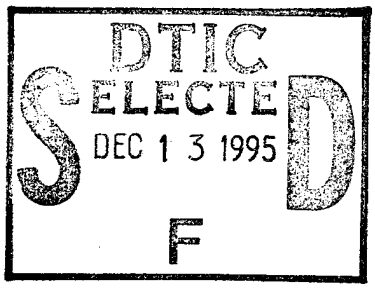
TITLE: DEVELOPMENT OF AN LSTAT VENILATOR



PRINCIPAL INVESTIGATOR: David O. Warner, M.D.

CONTRACTING ORGANIZATION: Mayo Clinic
Rochester, Minnesota 55905

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David O. Warner, M.D.

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Mayo Clinic
Rochester, Minnesota 55905

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13. ABSTRACT (Maximum 200 words)

There is a critical need for a small, portable device to provide ventilatory support to critically-ill battlefield casualties. The goal of this work is to develop a prototype ventilator suitable for incorporation into the LSTAT unit. In this time period the initial research and design phase has been completed, and an initial prototype fabricated. This prototype has successfully demonstrated the feasibility of this concept. Contacts have been initiated and working relationships established with other contributors to the LSTAT project, so that all components may be optimized for final incorporation into the finished unit. Work is continuing to refine the design and to implement servo control.

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FOREWORD

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Principal Investigator's Signature

9/29/95
Date

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I. Introduction

There is a critical need for a small, portable device to provide ventilatory support to critically-ill battlefield casualties. No such device currently exists which can operate independently of compressed gas sources and line power.

The original goal of this proposal was to perform a feasibility study to demonstrate that the construction of this device was possible. Optional future tasks included later collaboration with a ventilator manufacturer to fabricate a device suitable for production. A protocol describing four tasks, including establishing ventilatory requirements, fabrication of a prototype, and testing in both mechanical lung models and animals was submitted in March 1994 and approved for funding. At a kickoff meeting for the LSTAT project at Walter Reed in July 1994, it became apparent that the expectations of this Army concerning this original proposal had considerably changed. The goal stated at this meeting by ARPA and the Walter Reed Division of Combat Casualty and Trauma Research was now to develop a finished version of the ventilator for incorporation into the LSTAT unit within a short timeframe (2 to 3 years). A detailed specification sheet was also provided. In response, contact was initiated with a ventilator manufacturer (Omni-Tech Medical), and a modification to the original proposal that would meet the current needs of the project was prepared (see attached letter dated 20 Sept., 1994 and modified proposal, Appendix I), including the additional funding required for this expanded scope of work. In the meantime, funding for the original proposal was awarded, commencing 1 Oct. 1994.

In an electronic mail note dated Nov. 11, 1994 I was notified that the contract modification was approved. Based on this information, I began working with Omni-Tech on a limited basis, pending funding of the modification. By April 1995, funding of the modification had not yet materialized, yet all parties were anxious to proceed. I requested permission from the contracting office in April of 1995 to modify the original proposal, tasking Omni-Tech to fabricate the prototype that would demonstrate feasibility. The subcontracting agreement was concluded on August 15, 1995. Even without funding of the modification, we continued to make significant progress in ventilator development (as described below), including contacts with both Walter Reed and Northrop-Grumman, prime contractor for the LSTAT program.

In an electronic mail note dated 18 August 1995, Brenda Fischetti has informed me that the modification has been funded pending review by MRMC legal counsel, and that funding should be forthcoming within one week. Based on this understanding, I have structured this progress report to reflect the tasking of the modified proposal, which in turn reflects reality. Because of the delays engendered by funding uncertainty, I am dating effort from 1 July to reflect a "first quarter" report, although it should be recognized that development has been proceeding on a limited basis for a longer period of time.

II. Body

II.A. Summary.--In this first period, Task IA (Research and Design) has been completed, and Task IB (Initial Prototype Fabrication) has commenced. An initial prototype is now functional.

II.B. Task IA - Research and Design.--Several design meetings have been held between Omni-Tech Medical and Mayo at both sites regarding critical design issues. A meeting of parties involved in ventilator development was held in March 1995 at Walter Reed which was very productive. Mayo and Omni-Tech have also traveled to Northrop-Grumman, contractor for the LSTAT unit, to coordinate ventilator design with the rest of the LSTAT unit. Further meetings have been held with suppliers such as Gast, who will supply the compressor unit for the ventilator. Thus, active collaboration among parties responsible for ventilator development has been in evidence.

A major decision reached in June 1995 with the concurrence of Walter Reed was to proceed with a distributed design of ventilator components; i.e., rather that being physically self-contained, ventilator components such as the air compressor should be distributed throughout the LSTAT sled according to optimal functionality, size, and weight considerations. This will necessitate close coordination of design among Northrop and the Mayo team, which has commenced.

Progress to date will be categorized according to major areas of design challenge.

II.B.1. Compressor.--An initial visit to Gast Inc., the leading supplier of medical gas compressors, led to purchase of an existing compressor to provide a source of compressed air. When applied to the prototype (see description below), this compressor was able to provide approximately half of the required ventilatory parameters (minute ventilation of 10 l/min, working pressure of approximately 10 psi), with a power requirement well within budgeted power expenditures (40 watts). Based on this encouraging result, engineers from Omni-Tech met again with Gast engineers and have secured another unit which we believe will meet requirements. Evaluation of this unit will be complete by the end of September 1995, and further modifications discussed with Gast if necessary. Once a final unit is chosen, determination of the size of gas reservoir required for optimal function can proceed. The initial optimal working pressure for the system has been targeted at 20 psi.

The status of the on-board oxygen generator (OBOG) is apparently uncertain. For the moment, we and Northrop are assuming that a high pressure source of oxygen will be available, whether from the OBOGs, compressed gas, or other technology. Design work has commenced on a system to blend compressed air and oxygen in desired proportions. This is a challenge, as there may be significant variations in the working pressure for both.

II.B.2. Power Supply.--Based on the distributed design concept, it has been decided to utilize the LSTAT on-board battery and line voltage power supplies rather that use a separate dedicated unit contained within the ventilator itself. The power budget for the ventilator components has been set at approximately 86 watts.

II.B.3. Pneumatic Control.--The design for pneumatic control will be based on an existing design developed by Omni-Tech. The control is in the process of being modified to account for a lower working pressure (20 vs. 50 psi), to electronically regulate inspiratory flow, and to provide for end-inspiratory hold.

II.B.4. Electronic Control and Display.--An initial simple control system has been fabricated to permit initial testing. Extensive discussion has been initiated regarding servo control issues (see Appendix II for examples of planning documents). It is apparent that the major challenge is to determine if the proper response to changes in sensed parameters such as end-CO_2 involves a ventilator response (e.g., increase minute ventilation) or an operator response (e.g., replace the endotracheal tube that has just fallen out). Currently we plan to incorporate at least two levels of control: an automatic mode for servo control, and a manual mode (or several levels of manual modes) that could override servo control if an expert operator is available (see Appendix II).

Consistent with the distributed design concept, the final design will include control systems within the overall LSTAT control unit, which, conveniently, utilizes the same microprocessor as the original ventilator unit. The ventilator display will also be incorporated into the overall LSTAT display.

II.B.5. Anesthesia Capabilities.--We have been asked by Walter Reed to investigate the possibility of including the capability of delivering volatile anesthetics through the ventilator unit. A considerable effort has been expended evaluating the suitability of available anesthetic vaporizers for this purpose. Units evaluated include the Anaquest Draw-over vaporizer and Tech 5 vaporizer for in-line use in the low-pressure circuit and a high-pressure Siemens vaporizer. None of these units are suitable. Because of wide fluctuations in delivered anesthetic concentrations with changes in airway pressure, the low-pressure vaporizers would be dangerous when used in the low-pressure circuit as proposed. The Siemens unit is specific to the Siemens Servo 900 ventilator design and will not function properly with our ventilator design.

We currently feel that the most appropriate solution is to use the LSTAT ventilator to drive a bellows as part of a separate dedicated anesthesia module.

C. Task IB. - Initial Prototype Fabrication.--An initial prototype has been fabricated for testing purposes. Drawing approximately 40 watts, this unit provides approximately half of the required minute ventilation and is relatively insensitive to patient conditions. This initial prototype will be modified as the design process proceeds to incorporate new features. Figure 1 shows a block diagram of the current prototype.

Upon the request of Northrop, a second prototype is being fabricated for demonstration purposes in the current version of the LSTAT prototype. This unit will be used primarily for demonstration purposes and to assist in the design process for the optimal distribution of ventilator components throughout the sled.

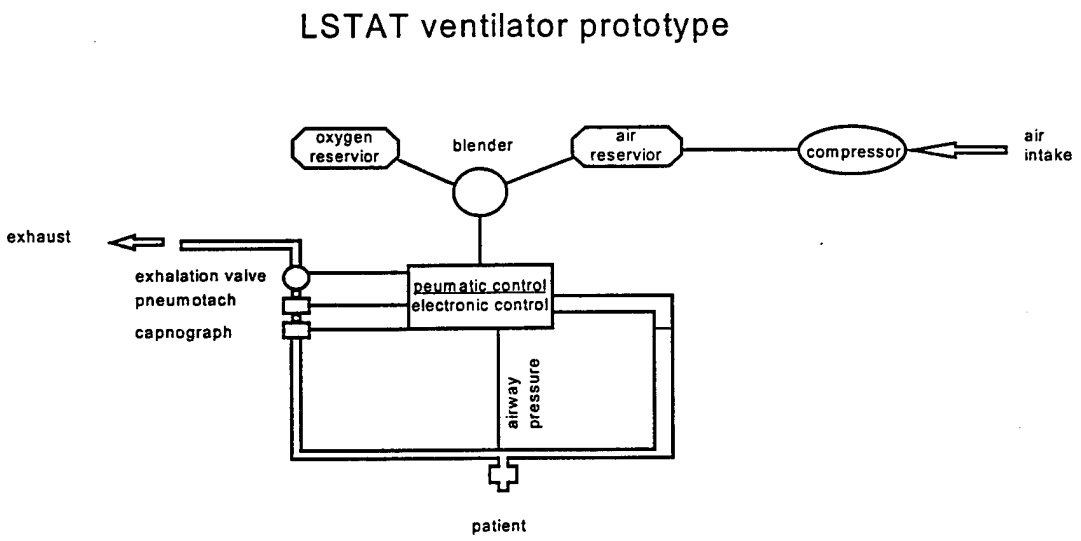

Figure 1.--Block diagram of current prototype

III. Conclusion

Development of the LSTAT ventilator is proceeding according to schedule, with excellent working relationships established between all parties involved. The feasibility of the concept has now been demonstrated. Further work on refining a pre-production version of the ventilator, including servo-control capabilities, will continue, focusing on key design issues as outlined (see Appendix II).

Appendix I - Modified Proposal

Mayo Clinic Rochester, Minnesota 55905 Telephone 507 284-2511

David O. Warner, M.D.
Department of Anesthesiology

September 20, 1994

Dr. Richard Satava
ARPA/MTD
Advanced Research Projects Agency
3701 North Fairfax Drive
Arlington, VA 22203-1714

Dear Doctor Satava:

Enclosed is a draft of a revision to the proposal entitled "Development of a Portable Microventilator". As we have discussed, it has become evident that our original proposal will not meet the current needs of the LSTAT ventilator as defined by Walter Reed Army Institute of Research (WRAIR), Department of Combat Trauma, Division of Surgery. The original proposal was for a simple design suitable for stabilization and transport. Current specifications describe a versatile device that will be used not only for stabilization and transport, but to meet the needs for mechanical ventilation throughout the perioperative period, including the delivery of anesthetic gases. To meet WRAIR specifications, a considerably more sophisticated approach is required. In addition, the original proposal was not designed to meet the desired timetable (basic design completed by April 1997). The aim of this original proposal was only to determine the feasibility of a concept, using a bench prototype, within this timeframe; it is now required that a finished prototype that meets the size and weight requirements of the LSTAT be developed by this time. This was described as an optional future task in the original submission. In short, the needs of the LSTAT program and WRAIR have evolved considerably since the submission of the original proposal, requiring a considerable expansion in the scope of the project.

We have initiated discussions with Omni-Tech Medical of Topeka, KS, a company with considerable experience in the design and production of small ventilators. We have also conferred with the personnel at WRAIR who have been actively involved in the development of this device. Based on these interactions, we have developed a revised proposal that we believe can meet the needs of the project, representing a collaborative effort between Mayo and Omni-Tech, with assistance from WRAIR. The aim of this proposal is to deliver a prototype that will meet the basic needs of the LSTAT project by the fall of 1996 (work described in Tasks 1 and 2). Optional tasks (tasks 3 and 4), requiring an additional 24 months of development, would concentrate on adding advanced capabilities, such as measurement of oxygen consumption, that are currently not feasible, but are highly desired by WRAIR personnel, and represent cutting-edge technology yet to be developed. In essence, we are skipping over the feasibility studies described in the first two years of the original proposal, and proceeding directly to development of a pre-production prototype. This revised proposal has several major advantages over the original:

1) The revised proposal aims to meet the specifications promulgated by WRAIR subsequent to the time of submission of the original proposal. The basic design described in the original proposal cannot meet these requirements.

2) The original proposal was limited to a feasibility study, whereas the revised proposal aims to produce an actual working prototype that meets LSTAT size and weight requirements.

3) The assistance from WRAIR should ensure that the ventilator will indeed meet military requirements, and will allow continuous input by military staff. Furthermore, the contacts afforded by WRAIR with technology vendors has and will continue to greatly benefit the design process.

4) The inclusion of industry collaboration from the outset (not envisioned in the original proposal until much later in the design process) will allow proper documentation and procedures required by the FDA and other regulatory bodies that will speed eventual approval of the device for clinical use. Recent military experience with small ventilators demonstrates that this consideration is especially important. Proper observance of these procedures will also speed technology transfer to the civilian sector. Furthermore, factors such as reliability and engineering for environmental constraints will now be considered as an integral part of the design process.

5) Plans for technology to be developed by other ARPA contractors regarding oxygen production and the measurement of respiratory gasses are now incorporated as an integral part of the design process.

Expansion of the scope of the project will also require an expansion of the resources required for its successful completion. We have prepared what we believe to be a reasonable preliminary estimate of the costs involved to complete the first 2 tasks (covering the first 2 years of development), totalling approximately $900,000. Under this arrangement, Mayo would serve as the prime contractor, with Omni-Tech serving as a subcontractor. Details of the arrangement are found in the body of the revised proposal. Please let me know if funding in this range would be feasible. I again want to emphasize that although the total amount exceeds that originally proposed, so too does the scope and ambition of the proposed work.

We are prepared to proceed with signing the current version of the contract forwarded to us by the contracts officer to perform the work described in the original proposal, so as to access the funds allocated for this fiscal year, with the recognition that modification of the contract will be necessary to meet your needs.

I remain excited about commencing work on this project, and am more optimistic than ever that the device can be built by the team we are assembling. I remain committed to developing a ventilator that will not only meet your basic needs, but push the envelope of the possible.

Sincerely,

David O. Warner, M.D.

Development of a portable microventilator

Revision #1

A proposal submitted in response to

BAA 94-14: ADVANCED BIOMEDICAL TECHNOLOGY

To Dr. Richard Satava
ARPA/MTD
Advanced Research Projects Agency
3701 North Fairfax Drive
Arlington, VA 22203-1714

David O. Warner, B.S.E.E., M.D.
Mayo Clinic and Foundation
200 1st ST SW
Rochester, MN 55905

tel. (507) 255-4288
fax. (507) 255-7300
dowan@hypnos.mayo.edu

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A. Summary

There is a great need for a small, portable ventilator, suitable for field use, to provide ventilatory support for critically-ill combat casualties. In addition, this microventilator would have wide civilian application to patients requiring mechanical ventilatory support in out-of-hospital settings. The purpose of this project is to produce a small, portable ventilator for use in the LSTAT. The project is organized to accomplish four tasks. In **Task 1**, an initial prototype will be developed, with the goal of meeting the ventilatory requirements, size limitations, and energy constraints of the LSTAT project. **Task 2** will concentrate on further development of the prototype to confirm safety and reliability of this basic design, including testing in animals. In **Task 3 (optional)**, enhancements will be added to the basic design, especially those to provide closed loop and remote operating capabilities. In **Task 4 (optional)**, a production model of the ventilator will be perfected and the unit fully integrated into the LSTAT package. Development of this ventilator will be a collaborative effort among Mayo and Omni-Tech Medical of Topeka, KS, with support from Walter Reed Army Institute of Research (WRAIR).

B. Statement of Problem

Many medical and surgical patients require mechanical ventilation of the lungs at some point in the course of their illness. In military medical practice, battlefield casualties frequently require such support before and after surgical therapy. In fully-equipped surgical units with available generator power and oxygen supplies there is a wide variety of ventilators available to meet this need. However, in the combat environment, such facilities may not be available. In addition, casualties may need to be transported while receiving ventilatory support, rendering most currently available ventilators impractical. Furthermore, because battle casualties often sustain chest wounds and require ventilatory assistance, a ventilator may provide critical support immediately after injury and thus extend the "golden hour", sustaining the patient until transport is tactically feasible. Thus, a need exists for a small, portable ventilator that can provide ventilatory support to these critically-ill patients. Furthermore, because personnel trained in the management of artificial ventilatory support may be scarce, it would be desirable to employ servocontrol mechanisms so that the ventilator can, within operator-specified limits, adjust itself to the needs of the patient.

Although currently-available ventilators are capable of generating sophisticated patterns of ventilation, most require line voltage and sources of compressed air and/or oxygen to function, requirements that make them impractical for field use. For example, a recent report described the use of the Oxford Mark 1 ventilator during the deployment of Fleet Hospital Five during Operation Desert Shield/Desert Storm (Military Medicine 158: 538-542, 1993). Although the device provided adequate ventilation, 3 fully-sized H cylinders were required daily to supply the driving gas, a requirement recognized as a significant limitation by the authors.

In addition to these needs for initial stabilization and transport of battlefield casualties, the armed services require a ventilator for general purpose use. It would be desirable from many standpoints if the device could also provide ventilatory support for all phases of casualty treatment, including the delivery of anesthesia and postoperative ventilatory management.

C. Innovative Claims

The overall objective of the proposed research is to determine the feasibility of a microventilator that will meet military and civilian needs described above, and to develop this ventilator for production and incorporation into the LSTAT system. The goal is to provide a device that satisfies the requirements promulgated by the Walter Reed Army Institute of Research (see attached document). Four innovative features will characterize the ventilator prototype to be developed:

- small size
- ease of use
- lack of dependence on sources of compressed gas or line power
- servo control utilizing parameters such as minute ventilation or oxygen consumption.

D. Technical Plan

D.1. Technical Rationale

The two components of any ventilator are 1) a source of gas pressure to inflate the lung, and 2) a system to control the application of this pressure to the airways.

D.1.a. Pressure source.--The primary challenge of this project is to devise a source of pressure sufficient to provide ventilation without the use of compressed gas. The efficiency of this source must be sufficient to function for two hours using internal rechargeable battery power, so that the choice of power source is critical to the design. The device will be required to deliver a minute ventilation of 15 $l \cdot min^{-1}$ to a respiratory system model with a total respiratory resistance of 20 $cmH_2O \cdot l^{-1} \cdot s$ and a dynamic compliance of 0.02 $l \cdot cmH_2O^{-1}$. The device must be accommodated within the size constraints of the LSTAT module (see attachment).

Possible approaches include:

a) High pressure/low flow: An example of this approach would be a compressor capable of generating relatively high pressure at low flows, used to drive a piston, bellows, or venturi device. Required flows could be significantly less than those required for peak ventilation, but must be delivered at high pressure.

b) Low pressure/high flow: An example of this approach would be a turbine or piston sufficient to meet the peak flow demands of ventilation (approximately 1 $l \cdot s^{-1}$ at pressures of approximately 50 cmH_2O). Requirements of the LSTAT are such that approaches such as continuous flow with intermittent expiratory occlusion are not suitable.

A primary task will be research to determine what technologies or approaches are currently available that could be utilized in the design. Based on this research, an initial approach can be determined and preliminary design drawn up.

Based on knowledge of the energy needed to inflate the lungs, and the limits of current battery technology, battery-powered operation should be feasible. The rate of energy expenditure to ventilate the lungs of normal postoperative surgical patients is approximately 20 joules·min^{-1}; the rate may exceed 100 joules·min^{-1} in diseased lungs. The capacity of current-available battery systems varies widely with the materials used, ranging from 250 Kjoules/dm^3 for simple lead-acid batteries to 1400 Kjoules/dm^3 for Li-organic cells, expressed as total capacity per unit volume of battery. Thus, even assuming a low efficiency of operation of 5%, a battery with 1 dm^3 volume should provide sufficient power to approximately 2 (lead-acid) to 12 (lithium) hours of operation to provide 100 joules·min^{-1}.

D.1.b. Control system.--The control system will apply pressure generated by the source in a controlled manner to the airway opening. The initial system must use a microprocessor-based technology to deliver a preset minute ventilation at a given breathing frequency. It must include sensors such as airway pressure monitoring that will be incorporated into later versions to ensure safe operation. As the ability to monitor respiratory flows will be integral to later versions of the ventilator, a flow-sensing device should be included. The initial version must also include intermittent mandatory ventilation capability. Initial implementation of control algorithms could be made on a PC platform to facilitate later modifications.

D.1.c. Feasibility. It should be acknowledged that it is not certain that it is physically possible with current technology to fabricate a device that can sustain ventilation without supplies of compressed air using battery power over a reasonable length of time. However, based on the technical rationale, we believe that there is sufficient reason for optimism that this attempt to demonstrate the feasibility of this approach is justified.

D.1.d. Considerations for use in Human Subjects. Because this device is intended to be used in human subjects under field conditions, durability and reliability of the design are crucial. The design must meet the standards imposed by the military regarding shake testing, range of environmental stresses, etc. Furthermore, proper recordkeeping during the development will be important in the approval process by the FDA and other regulatory bodies.

D.2. Approach

Development of this ventilator will be a collaborative effort between Mayo and Omni-Tech Medical of Topeka, KS, with assistance from Walter Reed Army Institute of Research (WRAIR). Mayo will function as prime contractor, with Omni-Tech as a subcontractor, and WRAIR providing support as needed. This approach best utilizes the strength of each participant. WRAIR has been actively engaged in this project, developing control algorithms for the ventilator and investigating technologies that may be of use. Omni-Tech has considerable experience in the design and production of small ventilators. Of importance, they have expertise regarding engineering of medical products for durability and reliability, and infrastructure in place to satisfy the requirements of bodies such as the FDA, which will be important for the device to receive approval from the FDA. Mayo has expertise in the physiology of mechanical ventilation and its control, will be involved in all aspects of development, and will be primarily responsible for testing.

Development will be organized to accomplish the following tasks.

Task 1.--Initial Prototype Design

Task IA: Research and Design -- 4 months are allocated for the initial research and design phase. At the conclusion of this period, a preliminary design for the basic prototype should be agreed upon by all parties.

Task IB: Initial Prototype Fabrication -- 14 months are allocated for construction and testing of the initial prototype pressure source and simple controller. At the conclusion of this period, a functional, PC-driven prototype that will demonstrate the feasibility of the design will be fabricated. Initial tests in normal animals will be performed to demonstrate that the device can meet the ventilatory demands of normal animals.

It should be recognized at the outset that Task 1 is the most critical. Indeed, there is no guarantee that the ventilator desired by WRAIR can be designed to fit within the size and weight criteria specified by the LSTAT program.

Task 2: Prototype Development

After demonstration of prototype feasibility, the next step will be to explore the safety and reliability of the basic design, with attention to quality control issues. Incorporation of basic alarms and safety devices will be important. Of paramount importance, the pressure-generating and flow-control systems must be engineered to ensure reliable operation under field conditions. Concurrently, testing in experimental animal models of adult respiratory distress syndrome will be conducted to evaluate performance in diseased lungs.

Six months are allocated for Task 2. At the conclusion of this period, the basic prototype

should meet field testing standards imposed by the armed services and the basic requirements promulgated by WRAIR.

Optional Tasks

After development and testing of a suitable prototype, further tasks could be pursued as desired.

Task 3: Incorporation of Advanced Features

In Task III, more advanced features will be added to the basic design, including components designed by other ARPA contractors. Possible additions will include: 1) advanced sensor capabilities, such as respiratory gas measurements provided by ARPA contractors, 2) further development of closed-loop capabilities, 3) accommodation of oxygen enrichment technology provided by ARPA contractors, 4) advanced ventilatory modes such as pressure support ventilation, and 5) remote telemetry and control capabilities. Once incorporated, these features must be tested in animal models. It is also anticipated that further improvements on the basic design will be made over this period.

Twelve months are allocated for Phase III. At the end of this period, the ventilator should meet full specifications as promulgated by WRAIR, Division of Combat Surgery.

Task 4: Production Version and Integration with LSTAT

In this phase, a production version of the ventilator will be designed and fabricated, based on previous experience. Control systems will be integrated with the LSTAT unit to allow for remote control and telemetry. Testing on human subjects would commence. The details of this phase will depend on the experience with the previous phases, and the then current needs of the LSTAT program. The ability to deliver volatile anesthetics will be developed.

Twelve months are allocated for Phase IV. At the completion of this period, a production version of the ventilator should be available for full integration into the LSTAT and ready to begin the approval process by appropriate regulatory bodies for human use.

D.3. Summary of Technical plan and Deliverables

D.3.a. Objective

Determine the feasibility of the microventilator concept by developing and testing in living animals a prototype of a small, compact ventilator suitable for field use. Design goals include 1) small size, 2) ease of use, 3) lack of dependence on sources of compressed gas or line power, and 4) servo control utilizing parameters such as minute ventilation or oxygen consumption.

D.3.b. Statement of Work

Task 1.--Initial Prototype Design

Task 1A.--Research and Design. Determine optimal design and technologies.

Task 1B.--Initial Prototype Fabrication. Produce and test initial prototype.

Task 2.--Prototype Development. Further development of basic prototype to acheive basic specifications.

Optional Tasks

Task 3.--Incorporation of Advanced Features. Incorporate advance capabilities, including advanced closed-loop algorithms.

Task 4.--Production version and integration with LSTAT. Fabrication of final production version of ventilator, and full incorporation into LSTAT.

II.C. Deliverables

1. Quarterly technical and financial progress reports; final technical progress report.

2. Slide, hardcopy, and presentation material of technical progress as requested by ARPA; copies of preprints and reprints of any papers submitted for publication.

3. Full schematics and working drawings of ventilator prototype, including source code for servo algorithm.

D.4. Participants

D.4.a. General Description

Mayo -- The team at Mayo will function as the overall coordinator of the project. Specific duties will include coordinating the activities of other participants, ensuring that timetables and milestones are met, and testing of the ventilator in animals, and, if feasible, human subjects. As the principal expertise of Mayo lies in the physiology of mechanical ventilation, its principal responsibility will be to ensure that the ventilator meets the physiologic needs of patients.

Omni-Tech Medical-- Omni-Tech will be primarily responsible for the fabrication of the device, including pressure source and devices to regulate gas flow, electronic control systems, and the engineering of the final design. They will also be responsible for documentation of quality assurance data that will be eventually required for certification for use in human subjects.

WRAIR -- The team at WRAIR will function to ensure that the ventilator meets the needs of the Army in general and the LSTAT program in particular. The contacts of WRAIR with sources of technology that can be utilized in the ventilator will be especially important. The available expertise in programming will be valuable in developing advanced control algorithms.

D.4.b. Specific Responsibilities of Participants

Task 1A (months 1-4). All three participants will work closely together in the design phase. Identification of current or emerging technologies of potential use will be a key part of this effort. It is anticipated that Mayo will utilize its contacts in academia, WRAIR will utilize its contacts with DOD contractors and researchers, and Omni-Tech will utilize its contacts with industry to ensure that the best available tools are brought to bear.

Task 1B (months 5-17). Primary responsibility for the assembly of the initial prototype lies with Omni-Tech, with assistance from the other participants. Mayo will work closely with the Omni-Tech team, and commence animal testing During this phase, WRAIR will continue its development of control software.

Task 2 (months 18-24). Omni-Tech will continue prototype development with attention to issues of safety and reliability. WRAIR will work closely with the company to ensure that field standards are met, and implement control software. Mayo will continue testing of the prototype in living animals.

Task 3 (months 25-36). Under the guidance of WRAIR, Mayo and Omni-Tech will integrate advanced design features into the prototype. Features will be sequentially evaluated in animal

models by Mayo, and the design changed as required. All participants will work with other ARPA contractors developing oxygen delivery and respiratory gas monitoring technology, incorporating these devices into the ventilator.

Task 4 (months 37-48). Omni-Tech will continue to refine the design into one suitable for production. Mayo will ensure through animal and human testing that the ventilator can indeed meet the physiologic requirements of patients. WRAIR will coordinate ventilator function with the other needs of the LSTAT program, to ensure that it functions in harmony with other LSTAT components.

E. Business Plan

This technology would have numerous civilian applications, including medical transport, emergency medical services, and those patients requiring home ventilation. Development of such applications would be negotiated between Omni-Tech Medical, subcontractor to this proposal, and Mayo Medical Ventures. Mayo Medical Ventures is a subsidiary of the Mayo Foundation whose purpose is to realize the commercial potential of devices developed by Foundation staff.

F. Budget and Justification

F.1. General Comments

The budget provided covers the first two years of development (Tasks 1-2). The budget of the completion of the Optional Tasks (Tasks 3-4) would depend in some measure on the nature of the device, but should approximate in total amount that for the first two and one-half years.

F.2. Justification, Mayo Component

F.2.a. Personnel

Management.--Support is requested for the principle investigator, who will supervise and be responsible for all aspects of the work at Mayo, and will work closely with the subcontractor and WRAIR.

Technical support.--Support is requested for laboratory technical personnel. Responsibilities will include conducting all tests and evalutations of the device using both the mechanical lung model and living animals.

F.2. b. Equipment and Supplies

Purchase of animals.--20 dogs are requested in year 2 to test the ventilator prototype.

Supplies.--Funds are requested for general laboratory equipment and supplies.

F.2.c. Travel

Included are funds to cover the costs of trips per year to Washington, D.C. to present the ongoing work to sponsors and/or designees, and the cost of travel to Topeka, KS, to meet with the subcontractor. Allowance is also made for trips to vendors that may provide technology needed for the device.

F.3. Justification, Omni-Tech component (Subcontract from Mayo)

F.3.a. Personnel

Technical Support and Management.--Funds are requested for efforts of the Company President and Managing Director for cognitive, research and testing of the theory of operation of the power source and functional ventilator.

Engineering Time and Support.--Funds are requested to support the writing of software for the ventilator, development the mechanical portions of the interface devices and beginning the Hazards Analysis portion of the Design Control Procedures.

Administrative and Accounting Support.--Funds are requested for these activities, required to keep the program on schedule. In addition, reporting procedures within the company are necessary to keep adequate records for quality assurance, interactions with Mayo Medical Ventures, and FDA regulations.

F.3.b. Travel

Funds are requested for the Engineering Staff and Technical Support personnel for travel to Rochester, MN, Walter Reed Army Medical Center, and other locations related to the procurement of components for the ventilator power source.

F.3.c. Supplies

Funds are requested to purchase components to be used in fabrication of the device.

F.3.d. Profit

A margin based on costs is used to calculate a minor profit for the company to continue in business. This is calculated at a before tax rate of 15% of the previously noted budget items.

F.4. Summary of Proposed Budget, by Tasks and Deliverables

Task 1.--Initial Prototype Design

Task 1A.--Research and Design. Determine optimal design and technologies.

Period.--Months 1-4

Deliverables.

1. Schematic for initial prototype.

Total cost for this task.--$163,588

Task 1B.--Initial Prototype Fabrication. Produce and test initial prototype.

Period.--Months 5-17

Deliverables

1. Full schematics and working drawings of ventilator prototype.

2. Full report of performance characteristics of testing in mechanical lung models and living animals.

Total cost for this task.--$486,176

Task 2.--Prototype Development. Further development of basic prototype to acheive basic specifications.

Period.--Months 18-24

Deliverables

1. Full schematics and working drawings of ventilator prototype.

2. Full report of performance characteristics of testing in mechanical lung models and living animals.

3. Documentation of performance testing for reliability and durability.

Total Cost for this task.--$252,812

G. Appendix

G.1. Description of institution

Mayo Foundation is a not-for-profit foundation dedicated to clinical care, medical education, and medical research. The Foundation has a long history of participation in DOD projects, including the aeromedicine program begun in WWII by Dr. Earl Wood and continuing work by Dr. Barry Gilbert on several ARPA projects. The Human and Integrative Physiology Laboratory of the Department of Anesthesiology, headed since 1989 by the principle investigator, has extensive experience in studies of respiratory physiology in both animals and humans. In addition, the laboratory has previous experience in ventilator design and construction, having fabricated a high frequency oscillator in the early 1980's. The Mayo Section of Engineering has extensive experience in the fabrication of medical devices. The heavy clinical volume at the Mayo Clinic would provide ample opportunity for field testing of any finished ventilator unit.

G.2. Curriculum Vitae of Principle Investigator

Dr. David O. Warner received the B.S.E.E. degree in 1979 and the M.D. degree in 1983 from The Ohio State University, both magna cum laude. He completed an residency in Anesthesiology in 1988 that included two years of a research fellowship in pulmonary physiology. During this period he received the Balfour Award from the Mayo Foundation for outstanding research performed by a fellow. Since joining the Department of Anesthesiology as a staff consultant in 1988, he has pursued both clinical and research interests, which include pulmonary mechanics, airway smooth muscle, and respiratory muscle function while awake and anthetized. Extramural grant support has included an NIH FIRST award entitled "Anesthesia and the Respiratory Muscles" from 1988-1993. Since 1990 he has also served as principle investigator of NIH grant R01 HL45532 eintitled "Anesthesia and the Airways". He has published over 30 papers in peer-reviewed journals.

G.3. Animal Care

1. Description.--20 mongrel dogs of either sex will be used to test the ventilator prototype. The dogs will be anesthetized with pentobarbital through each experiment.

2. Justification for animal use.--Before this prototype would be used in human subjects, it is necessary to perform animal tests to ensure its safety and efficacy. Large dogs are chosen as approximating human size and ventilatory requirements, and because of the extensive experience of this laboratory and others with the respiratory system of this species. Also, the oleic acid model of lung injury is well-established in this species. The number of dogs required will depend on the performance of the prototype and the degree of performance enhancements required during its development. We estimate that a total of 20 dogs (10 normal, 10 with oleic acid injury) will be necessary.

Appendix II - Paradigm being used to develop servo algorithm

Causes of increases in airway pressure

Etiology	Signs	Options for responses (one or more)
I. Decreased chest wall compliance		
A. Patient effort	• Irregular or patterned, transient or sustained increases in Paw • Irregular plateau of capnogram	• Sedate/paralyze patient • Increase VE to decrease PaCO2 and drive to breathe • Change ventilatory mode to assist, IMV, etc.
B. Intrinsic chest wall injury (e.g., crush injury, hemothorax, pneumothorax)	• Regular, sustained increases in peak Paw • Regular plateau of capnogram; increased $PetCO_2$ (in the absence of other abnormality)	• Treat injury (e.g., reduce abdominal pressure, chest tube) • Change ventilatory pattern to reduce tidal volume while maintaining VE • Tolerate increased Paw as necessary to ventilate patient; consider accepting a lower VE
C. Extrinsic chest wall restriction	• Regular, sustained increases in peak Paw • Regular plateau of capnogram; increased $PetCO_2$ (in the absence of other abnormality)	• Identify restriction (clothing, etc.) and remove • Change ventilatory pattern to reduce tidal volume while maintaining VE • Tolerate increased Paw as necessary to ventilate patient; consider accepting a lower VE
D. Small patient size (i.e., normal specific compliance, low absolute compliance)	• Regular, sustained increases in peak Paw • Regular plateau of capnogram; decreased $PetCO_2$ (in the absence of other abnormality)	• Reduce VE to an appropriate level

II. Decreased lung compliance		
A. Lung injury (e.g., pulmonary edema, contusion)	• Regular, sustained increases in peak Paw • Regular plateau of capnogram with possible increases in slope; increased or normal $PetCO_2$ (in the absence of other abnormality)	• Treat lung injury (usually difficult) • Change pattern of ventilation to reduce tidal volume while maintaining VE • Tolerate increased Paw as necessary to ventilate patient; consider accepting a lower VE
B. Small patient size (i.e., normal specific compliance, low absolute compliance)	• Regular, sustained increases in peak Paw • Regular plateau of capnogram; decreased $PetCO_2$ (in the absence of other abnormality)	• Reduce VE to an appropriate level
III. Increased airway resistance		
A. Intrinsic (patient airways)		
1. Narrowed airways (i.e., pulmonary edema, bronchoconstriction)	• Regular, sustained increases in peak Paw; significant difference between peak Paw and plateau Paw • Regular plateau of capnogram; usually increased slope, may be increased $PetCO_2$ (in the absence of other abnormality)	• Treat condition • Change pattern of ventilation to reduce mean inspiratory flow while maintaining VE • Increase expiratory time to allow for full expiration
2. Obstructed airways (i.e., foreign body, trauma)	• Regular, sustained increases in peak Paw; significant difference between peak Paw and plateau Paw • Regular plateau of capnogram; usually increased slope, may be increased $PetCO_2$ (in the absence of other abnormality)	• Remove obstruction • Change pattern of ventilation to reduce mean inspiratory flow while maintaining VE • Increase expiratory time to allow for full expiration

B. Extrinsic (artificial airways)		
1. Patient-ventilator interface (i.e., endotracheal tube or LMA;obstruction, kinking, or malposition)	• Regular, sustained increases in peak Paw; significant difference between peak Paw and plateau Paw • Regular plateau of capnogram; usually normal slope; may be increased $PetCO_2$ (in the absence of other abnormality)	• repair interface • Change pattern of ventilation to reduce mean inspiratory flow while maintaining VE • Increase expiratory time to allow for full expiration
2. Ventilator circuitry (i.e., malfunction of expiratory valve)	• Depends of site of obstruction; with obstruction of expiratory limb, progressive increase in peak and trough Paw	• repair circuitry

Causes of decreased peak airway pressure

Etiology	Signs	Options for responses (one or more)
I. Increased chest wall compliance		
A. Trauma (i.e., flail chest)	• Regular or irregular, constant or intermittant decrease in peak Paw	• Repair trauma • No adjustment may be required, or; Increase tidal volume to maintain VE
B. Large patient size	• Regular, sustained decreases in peak Paw • Regular plateau of capnogram; increased $PetCO_2$ (in the absence of other abnormality)	• Increase VE to an appropriate level
II. Increased lung compliance		
A. Large patient size	• Regular, sustained decreases in peak Paw • Regular plateau of capnogram; increased $PetCO_2$ (in the absence of other abnormality)	• Increase VE to an appropriate level
III. Airway leak		
A. Intrinsic		
1. Trauma (i.e., bronchopulmonary fistula	• Regular or irregular, constant or intermittant decrease in peak Paw • Probably increase in $PetCO_2$ • Significant discrepancy between inspiratory and expiratory Vt	• Repair trauma • Increase inspiratory minute ventilation to maintain adequate ventilation
B. Extrinsic		
1. Patient-ventilator interface (i.e.,	• Regular or irregular, constant or	• Recognize problem and fix interface

endotracheal tube or LMA; incomplete seal, improperly placed ETT)

intermittant decrease in peak Paw

- Increase or decrease in $PetCO_2$; may be absent if expiratory flow is sufficiently small
- Significant discrepancy between inspiratory and expiratory Vt

2. Ventilator circuitry (i.e., incompetant expiratory valve, circuit disconnect)

Appendix III - Current design issues

(working document)

10 September, 1995

Current Design Issues - LSTAT Ventilator

1. Compressor

- Optimization by Gast, as directed by Omni-Tech and Mayo
- Decide upon number of compressor heads; inclusion of head for suction or other uses vs. use of a separate compressor for these needs
- Method of providing high pressure O_2 source; status of OBOG vs. other methods of O_2 supply
- Safety of compressing O_2 at approx. 20-50 psi?
- Maximize efficiency of motor powering compressor; minimize size and weight
- Size and location of reservior
- Servo control of reservior pressure and motor speed
    - minimal holding pressure when not in use
- Pressure relief is already present for reserior
- Cooling system for unit itself - tubing wrap
- The reservior can act as a heat exchanger
- Does Northrop want to use another head for other uses? (vacuum, etc)

2. Pneumatic Control

- Consider larger gas channels and valving in control "block" to accomodate the probable lower working pressure available (20 psi vs. the current 50 psi)
- Incorporation of electronically-controlled valve to regulate inspiratory flow
- Incorporation of manual inflation control
- Incorporation of end-inspiratory hold (part of electronic control)

3. Electronic Control and Display

- Current unit (for Omni 2100) is adequate for initial testing purposes
- Consider simplest operator interface for final design
    - What settings should the operator specify? Suggest three levels of control; automatic, manual: basic and manual: expert.
        - *Automatic:* includes servo control algorithm (see below)
        - *Manual: Basic*: Specify tidal volume and breathing frequency, with default I:E ratio of 1:3 with set end-inspiratory hold (the ability to regulate inspiratory flow is essential to this mode). Default F_IO_2 = highest available. Default mode = IMV . Default alarm settings.

- *Manual: Expert*: Independent control of T_I, T_E, inspiratory flow, inspiratory hold, F_IO_2. Choice of ventilatory modes (Controlled, Assist Controlled, IMV). Control of alarm parameters
- What information should be displayed for the operator?
  - *Automatic:* Alarm information only
  - *Manual: Basic*
    - Basic performance (Peak airway pressure)
    - Set parameters (V_T, f)
    - Monitored physiologic parameters (end-tidal CO_2, O_2 saturation, expiratory V_E)
  - *Manual: Expert*
    - Performance (continuous airway pressure)
    - Set parameters (V_T, f, I:E, T_I, T_E, F_IO_2, ventilatory mode)
    - Monitored physiologic parameters (end-tidal CO_2, O_2 saturation, expiratory V_T or V_E)
- What alarms should be included?
  - Maximum and minimum airway pressure
  - Minimum O_2 saturation

- Servo Algorithm
  - Basic approach - Cadillac (WRAIR version) vs. Jeep (Mayo version)
  - The major difficulty is the reliability of the sensed information; any algorithm must include routines to determine the reliability of sensor data.
  - The most reliable sensed parameter is probably airway pressure, which does reflect an interaction between the patient and the ventilator. A problem is that if the patient has effort, there may be transient (or sustained) increases in airway pressure that may not reflect the actual delivered tidal volume. There is also a component of airway pressure that depends upon flow resistance of the respiratory system. These components could be minimized by incorporating an end-inspiratory hold and would make this measurement a more reliable indicator of delivered tidal volume.
  - At the current level of technology, the only other reliable options for sensor technology that will be applicable at the battlefield level are the expiratory tidal volume and the end-tidal CO_2, and even these have significant limitations.
  - One approach would be to start with a default setting (e.g., flow = 0.6 l/min, T_I = 1s, T_E = 3s, f = 15, V_E = 9) and adjust from there. Possibilities?
    - Fix a max and min airway pressure. For example, if Paw > Paw_{max}, decrease inspiratory flow by a Δ and decrease T_E by an amount to maintain delivered minute ventilation (decrease V_T). If Paw < Paw_{min}, increase inspiratory flow by a Δ (increase V_T) and allow minute ventilation to increase correspondingly.
    - Evaluation of the expiratory tidal volume could be used to refine these measurements, the idea being to maintain a range of V_E that would suffice for most patients.

- End-tidal CO_2 could also be included, although this has real potential problems
- A major task will be to think of all the possbilities and attempt to adapt the system; this may or may not be possible, especially since the proper response depends on the source of the problem. For example, I can think of at least 5 reasons for increases in airway pressure beyond a set limit:
  - Patient effort (effectively ↓ing chest wall compliance)
  - ↓ lung compliance or ↓ chest wall compliance (secondary to injury)
  - ↑ airway resistance
  - Airway obstruction at any site
  - small lungs (small patient)
- Fuzzy control systems and patches might be appropriate to account for some of these possibilities

- Display - what is the best format to present information? How will this be integrated with other LSTAT displays?
- Alarms - Which? Smart or dumb? Silencing options? Methods to alert operator?

4. O_2 blending

- Assume that a reservior of O_2 will be available at approximately the same working pressure as the air supply (≈20 psi)
- Major challenges
  - account for the fact that the air and O_2 working pressures may not be identical, and may (indeed, certainly will) fluctuate
  - provide for electronic control of proportion
- Explore use of electronically-controlled proportioning valves along with regulators on both air and oxygen reserviors; what is currently available?

5. Anesthesia capabilities

- At this point, to our knowledge there is no available technology that can be used to easily provide in-line anesthetic vaporizer capability.
- Best approach would be to use the LSTAT ventilator to drive a bellows as part of a separate anesthesia module.

6. Other Issues

- IMV capability - adaptation of current capability - how to regulate and conserve inflowing gas to reservior? Just use a default settting for IMV flow?
  - The IMV system could be mounted on the front cowling and could do double duty as a bag ventilation system or a CPAP system
    - Manual needle valve to regulate flow, based on cowling

    - Manual switch between IMV (low, regulated flow) and bag ventilation (high, nearly maximal flow) modes
    - Pressure connection between bag and exhalation valve so that when the bag is compressed, the exhalation valve is closed. The manual switch could also control this connection. (How to provide CPAP - maybe a three position switch?)
- Location of components in breathing circuit; desirability of monitoring close to patient vs. convenience in mounting components. Also need to determine ergonomics of interface between patient and sled. For example, what will be the arrangement of components in the cowling to pass through from the ventilator to the patient connections? Components in question include:
    - pneumotachograph
    - capnograph head (will have to be at patient site)
    - expiration valve - OK to be mounted on cowling.
- What components should be disposable? What components need to be cleaned?